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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/904,968 | 07/13/2001 | Gregory G. Germino | JHU1680-2 | 3795 |

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| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

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|---|---|
| 08/29/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/904,968 | GERMINO ET AL. | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 January 2008 and 29 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,16,18,19,25,28-37,39-42,44,48-52,55-61,76 and 78-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,16,18,19, 25,28-37,39-42, 44,48-52,55-61,76,78-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/24/08 and 5/29/08 have been entered.

2. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the application in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn.

3. Applicant states on page 12 of the remarks filed 1/24/08 that the examiner found a limitation with SEQ ID NO: 3 in the first amplification product to be free of the art. However, this is not an entirely accurate representation of the examiner's statement of allowable subject matter. The examiner stated that "Thus, methods and products which require a primer **consisting of** instant SEQ ID NO: 3 are free of the prior art (emphasis added, see final office action 8/27/07)." In the claims before the office at this time, applicant has amended the claims to recite a primer that "includes at least SEQ ID NO: 3" which is broad open language equivalent to "comprising." There is no guidance as to how much can be added onto SEQ ID NO: 3 such that it would retain the unexpected property of being able to discriminate between PKD1 genes and PKD1 homologues. Thus, the recitation in the claims now is not commensurate in scope with the unexpected property that was referred to when the examiner discussed the fact that primers

consisting of SEQ ID NO: 3 and any combination requiring such a primer would be free of the art.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 3, 4, 16, 18, 19, 79, and 80, and confusing because the claim limitations conflict with one another. ON the one hand, the claim requires that the primers hybridize to "a sequence flanking and within fifty nucleotides of" one of the gene sequences set forth, for example nucleotides 2043-4290 of SEQ ID NO: 1. This means that the primer would be upstream or downstream of this region, within fifty nucleotides of the range. For example a primer that hybridizes to any of nucleotides 1993-2042 at the 5' end of the gene sequence, and primer which hybridizes within fifty nucleotides 3' to 4290. However, the claim also requires that one of the primers includes SEQ ID NO: 3. This primer occurs at nucleotides 2043-2071 of SEQ ID NO: 1, thus it is within nucleotides 2043-4290, NOT flanking it. The claim requires that the primers are flanking AND within fifty nucleotides of the regions of SEQ ID NO: 1, and so the requirement that one of the primers is SEQ ID NO: 3 conflicts with this requirement to the extent that no meaningful art rejection of the claims could be formulated.

Claim 18 depends from cancelled claim 17. Thus, claim 18 is rejected as being incomplete (See MPEP 608.01(n)(V)).

***Claim Rejections - 35 USC § 112***

5. The rejection of claims 1-4, 16 and 19 for lack of written description is WITHDRAWN in view of the amendment of claim 1 to delete the requirement that the recited primers do not hybridize to a PKD1 gene homolog sequence.

6. The rejection of claims 1-4, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement is WITHDRAWN because the current claims do not require that the claimed primers can be used to specifically amplify PKD1 gene having SEQ ID NO: 1 and not PKD1 gene homologs, does not reasonably provide enablement for additional primers that have this property.

7. Claims 25, 28-37, 39-42, 44, 48-52, 55-61, 76, 78, 81, 82, 83, 84, 85, and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the invention and breadth of the claims**

Claim 25 recites a method for detecting the presence or absence of a PKD1 polynucleotide in a sample, and concludes with identifying the presence or absence of an unidentified mutation in a second amplified product "wherein the presence of a mutation is indicative of a PKD1-associated disorder."

Claim 44 recites a method for identifying a subject at risk for autosomal dominant polycystic kidney disease, includes steps which lead to identifying the presence or absence of an

unidentified mutation in a second amplified product wherein the mutation is "indicative of ADPKD."

Claim 60 is similar to claim 44 but recites a method of diagnosing an ADPKD in a subject, includes steps with lead to determining whether an amplification product has a mutation associated with ADPKD.

The claims encompass the identification of a mutation at any position within the amplified products. Further, the claims only recite one primer to be used, and so the amplified products are of unknown length- the PKD1 gene as give in SEQ ID NO: 1 is over 50,000 base pairs long.

All of these claims require the detection of mutations in the PKD1 gene that are associated with ADPKD or with any PKD1-associated disorder.

**Teachings in the specification and the prior art**

The specification provides an over fifty kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKD1 gene sequence (¶0054).

The specification does teach and exemplify that it is unpredictable whether mutations or polymorphisms in the PKD1 gene will be associated with disease, specifically teaching in ¶ 0054 that not all nucleotide variations in SEQ ID NO: 1 will correlate with the signs and symptoms characteristic of a PKD1 associated disorder, and indeed the specification exemplifies in Table 2 that some mutations discovered segregate with disease and some do not. Thus, of all of the possible mutations that might be identified within the regions amplified in the rejected method claims, it is highly unpredictable which ones will be associated with disease. The specification has not provided a single mutation within this region that appears to be predictive of, let alone

diagnostic of disease. It is highly unpredictable whether or not such a mutation exists products amplified with SEQ ID NO: 3, and it is highly unpredictable whether one could identify such a mutation.

**Quantity of experimentation**

The quantity of experimentation required to practice the claimed invention, given the high degree of unpredictability in this art area is enormous. One would have to undertake extensive studies to first identify potential mutations or polymorphisms within any amplified region, which could include tens of thousands of nucleotides given that SEQ ID NO: 3 begins at nucleotide 2043 of SEQ ID NO: 1 and the claims are silent as to how much of SEQ ID NO: 1 would be amplified. Whether or not such polymorphisms or mutations exist is itself highly unpredictable, and if they do exist, the location and structure of these variants is highly unpredictable. Once mutations are identified, one would have to undergo further case controlled studies in patient and control populations to determine if the variants are predictive of any disease phenotype, and if so, which of the possible "PKD1 associated disorders" are predicted by the newly discovered mutation.

**Conclusion**

Thus, having carefully considered each of these factors, it is concluded that it would require undue experimentation to make and use the claimed invention.

8. Claims 25, 28-37, 39-42, 44, 48-52, 55-61, 76, 78, 81, 82, 83, 84, 85, and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification

in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of these claims sets forth identifying the presence or absence of a mutation in an amplification product that is indicative of or diagnostic of a PKD1-associated disorder or of ADPKD in particular. The amplification product in the claims is not defined, except for that the primers for amplification must include a primer comprising SEQ ID NO: 3, and the initial primer pair must hybridize under highly stringent conditions to SEQ ID NO: 1. Instant SEQ ID NO: 1 is over 50,000 nucleotides long, and so there are tens of thousands of mutational points possible in the unspecified amplified products. However, the claims do not include the detection of any of these possible mutations, only the ones that are "indicative" of a disorder or wherein the presence of the mutation identifies the subject is at risk or not at risk for ADPKD. Thus, the claims require the identification of a mutation that is within a subgenus of all possible mutations within the amplified products set forth in the claims.

The specification does teach and exemplify that it is unpredictable whether mutations or polymorphisms in the PKD1 gene will be associated with disease, specifically teaching in ¶ 0054 that not all nucleotide variations in SEQ ID NO: 1 will correlate with the signs and symptoms characteristic of a PKD1 associated disorder, and indeed the specification exemplifies in Table 2 that some mutations discovered segregate with disease and some do not. Thus, of all of the possible mutations that might be identified within the regions amplified in the rejected method claims, it is highly unpredictable which ones will be associated with disease. It is highly unpredictable whether or not such a mutation exists products amplified with SEQ ID NO: 3, and it is highly unpredictable whether one could identify such a mutation.

The specification discloses the complete structure of SEQ ID NO: 1. The specification does not describe how to identify by structure which mutations in SEQ ID NO: 1, disclosed or not, meet the limitations as set forth in the claim. Common structural attributes of the species in the genus are not described. All members of the genus have the same function, i.e. their association with disease, but no correlation between naturally occurring structures and this function have been disclosed. The question is whether one of skill in the art would be able to distinguish member of the subgenus (disease associated mutations) from other members of the genus of possible mutations within the amplified products.

The specification proposes to discover these mutations by amplification and sequencing of the gene from diseased individuals, and undertaking appropriate case controlled studies. The proposal to look for the requisite mutations and to confirm their association with disease is not a practical way to define the subgenus because finding a disease associated mutation could be successful only empirically. There is incomplete description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO: 1 predicts which possible mutational sites are disease predictive or associated. The general knowledge in the art concerning disease associated mutations does not provide any indication of how the structure of one disease associated mutation is representative of other unknown disease associated mutations.

The nature of mutations is that they are variant structures, and in the present state of the art, the structure of one disease associated allele does not provide guidance to the existence or structure of other alleles. In other words, the existence and structure of disease associated mutations is not predictable from the description of SEQ ID NO: 1. The description given is not adequate to allow one of skill in the art to distinguish mutations which are disease associated

from all possible mutations in the PKD1. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a the description is not representative of all of the genus and is insufficient to support the claims.

**Response to Remarks**

Applicant traverses the enablement rejection.

The rejection has been modified to address the amended claims, in particular to remove the portions of the rejection that are moot due to cancellation or amendment of the claims.

Applicant states that the claims were amended to include a primer with SEQ ID NO: 3, and to remove reference to other primers. This does not address the fact that the claims require detecting in the amplification products mutations associated with disease and encompass the detection of mutations at tens of thousands of possible positions, yet the specification does not provide any example or data to support such a claim. Applicant points to ¶0147 as teaching that a deletion of nucleotide 3336 is associated with a PKD1-associated disorder, however, this general assertion, absent evidence in the specification is not sufficient to appraise one of skill in the art that a reliable and predictable relationship exists between this mutation or any or all mutations in PKD1 and any possible PKD1-associated disorder, for the reasons discussed in the rejection.

The rejection is maintained.

***Conclusion***

9. If applicant amends claim 1 to recite that a primer consisting of SEQ ID NO: 3 is required, and if applicant overcomes the 112 2nd paragraph rejection set forth in this office action, claim 1 will be allowable, and thus all claims which depend from claim 1. Otherwise, upon amendment of claim 1 to overcome the 112 2nd paragraph rejection applicant is advised that further art rejections may be applied, depending on the requirements of the amended claims.

10. Klinger et al. (US 5654170) provides the sequence of the full length PKD1 gene, which comprises instant SEQ ID NO: 3. Klinger et al. also generically teach the selection of oligonucleotides that discriminate the PKD1 gene from PKD1 homologues (see their Col. 5, lines 40-55).

11. Rossetti et al. (American Journal of Human Genetics 2001; cited in IDS) teaches primer pairs for amplification of PKD1 genomic sequences. These primers are given in their Table 1.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is

(571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

August 29, 2008